REMARKS

Applicants respectfully request that the amendments be entered as they simplify issues for appeal.

I. Objection to Claims 3-6, 8, and 24-25

The Examiner objected to Claims 3-6, 8, and 24-25 "because the instant claims are partially drawn to non-elected inventions." (Office Action, page 3.) Claims 24 and 25 have been canceled, and therefore the objection as it pertains to Claims 24 and 25 is moot. In order to expedite prosecution, Claims 3 and 4 have been amended such that SEQ ID NO:2-8 and SEQ ID NO:10-16 are not recited. For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objection to Claims 3-6, 8, and 24-25.

II. Objection to Claims 5-6, 8, and 24

The Examiner objected to Claims 5-6, 8, and 24 "because of the following informalities, for clarity, the term 'a polynucleotide of claim #' should be replaced with 'the polynucleotide of claim #' since these polynucleotides have been previously defined." (Office Action, page 3.)

Claim 24 has been canceled, and therefore the objection as it pertains to Claim 24 is moot. In order to expedite prosecution, Claims 5-6 and 8 have been amended according to the Examiner's suggestion.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objection to Claims 5-6, 8, and 24.

III. Rejection of Claim 31 Under 35 U.S.C. § 112, first paragraph, written description

The Examiner rejected Claim 31 under 35 U.S.C. § 112, first paragraph, alleging that the claim contains "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Final Office Action, page 3.) In particular the Examiner alleged that claimed polynucleotides comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 are not adequately described because "the genus of polynucleotides comprised by the claim is a

large variable genus which can potentially encode proteins of diverse functions. The specification only discloses a single species of the genus, i.e. the polynucleotide of SEQ ID NO:9, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus." (Final Office Action, page 5.) The Examiner further states that "[t]here is no description of the mutational sites that exist in nature and there is no description of how the structure of the polynucleotide of SEQ ID NO:9 relates to the structure of any naturally-occurring variant." (Final Office Action, pages 4 and 5.)

The Examiner contends that "function" is required for adequate written description of the claimed polynucleotides (Final Office Action, page 3 and 5.) Applicants submit that "function" is not required to describe and use the claimed polynucleotides disclosed in the Specification. Furthermore, the Examiner has provided neither evidence nor sound scientific reasoning to support the allegation of lack of adequate written description.

Applicants note that this 35 U.S.C. § 112, first paragraph rejection on the basis of written description appears to be a new rejection as no written description rejection was made to Claim 10 in the Office Action mailed March 12, 2002, despite Claim 10 reciting an isolated polynucleotide comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:9-16. As the written description rejection of Claim 31 appear to be a new rejection, it is not proper that the Office Action mailed February 24, 2003 was made Final. The Examiner had the opportunity to make a written description rejection to Claim 10 in the Non-Final Office Action mailed March 12, 2002 but did not do so.

need to respond

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1 and 6-7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are described, for example, at page 18, line 28 through page 19, line 15. In particular, the preferred SEQ ID NO:1 variants (at least about 80%, at least about 90%, and at least about 95% amino acid sequence identity to SEQ ID NO:1) are described, for example, at page 20, lines 29-31. In particular, SEQ ID NO:9 variants (at least about 70%, at least about 85%, and at least about 95% polynucleotide sequence identity to SEQ ID NO:9) are described, for example, at page 21, lines 4-11. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1, 3, and 4 of the Specification. Chemical and structural features of MITP-1 are described, for example, in Table 2. Given SEQ ID NO:9, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:9 having at least 80% sequence identity to SEQ ID NO:9. The Specification describes (e.g., page 11, line 22 through page 12, line 28, page 45, lines 6-9, and Table 5) how to determine whether a given sequence falls within the "at least 80% identical" scope.

There simply is no requirement that the claims recite particular variant polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polynucleotide variants are defined in terms of SEQ ID NO:9 ("An isolated polynucleotide selected from the group consisting of . . . b) a polynucleotide comprising

a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9").

Because the recited polynucleotide variants are defined in terms of SEQ ID NO:9, the precise chemical structure of every polynucleotide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

A. The present claim specifically defines the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claim at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claim 31 recites chemical structure to define the claimed genus:

31. An isolated polynucleotide selected from the group consisting of. . .

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9. . .

From the above it should be apparent that the claim of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claim is defined in terms of the chemical structure of SEQ ID NO:9. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claim. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the

recited polynucleotides. The polynucleotides defined in the claim of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claim of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claim and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claim does not define a genus which is "large" and "variable"

Furthermore, the claim at issue do not describe a genus which could be characterized as "large" and "variable." (Final Office Action, page 5.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. (Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding polypeptides related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as PSST subunits of the NADH:ubiquinone oxidoreductase complex and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language"of the present claims recites, for example, polynucleotides comprising "a naturally occurring polynucleotide sequence having greater than 80% sequence identity to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9." This variation is far less than that of all potential PSST subunits of the NADH:ubiquinone oxidoreductase complex related to SEQ ID NO:1, i.e., those PSST subunits

of the NADH:ubiquinone oxidoreductase complex having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

C. The references cited by the Examiner are not relevant to the instant claim

Based on the references of Bork (Genome Research, 10:398-400, 2000) van de Loo et al. (Proc. Natl. Acad. Sci. U.S.A. 92:6743-6747, 1995) Seffernick et al. (2001; J. Bacteriol. 183:2405-2410), and Broun et al. (Science 282:1315-1317, 1998), it is suggested that "[t]he genus of polynucleotides comprised by the claim is a large variable genus which can potentially encode proteins of diverse function" and that "[t]he specification discloses only discloses a single species of the claimed genus, i.e. the polynucleotide of SEQ ID NO:9, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus" (Final Office Action, page 5). However, Applicants respectfully disagree.

The Examiner alleges that the "state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide." (Final Office Action, page 4.) However, in a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

Contrary to the assertions of the Office Action, the use of such sequence comparisons to predict protein function is supported by the Bork reference, cited by the Office Action. The Bork reference discloses a 70% accuracy rate in bioinformatics-based predictions. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics-based predictions.

van de Loo et al. describe the cloning of a fatty acyl hydroxylase based on sequence homology between certain fatty acyl hydroxylases and fatty acyl desaturases. In this example, the authors characterize fatty acyl hydroxylases and fatty acyl desaturases as catalyzing similar reactions (e.g., van de Loo et al., page 6743, right column, last paragraph), and conclude that the

reaction mechanisms of oleate 12-hydroxylase and oleate desaturase are similar based on the sequence homology between them (e.g., van de Loo et al., abstract). The Broun et al. reference relates to the same two enzymes, fatty acyl hydroxylases and fatty acyl desaturases. Since the functions of the oleate 12-hydroxylase and oleate desaturase described by van de Loo et al. and Broun et al. are similar,, it is not surprising that they share 67% sequence homology.

Accordingly if applicants had asserted that the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase, then the Examiner would have provided evidence that the assignment to this family of fatty acyl hydroxylases may be incorrect. However, applicants did not assert the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase or a fatty acyl desaturase. Therefore, the van de Loo et al. and Broun et al. references are irrelevant and are not scientific evidence that the polypeptide of SEQ ID NO:1 is not a member of the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex.

The Seffernick et al. reference describes two enzymes, a melamine deaminase and an atrazine chlorohydrolase, that are 98% identical, yet have different substrate specificities. These two enzymes belong to a class of bacterial amidohydrolases whose members are known to catalyze the hydrolytic displacement of amino groups or chlorine substituents from triazine ring compounds. Notably, the substrates of the two enzymes, melamine and atrazine, have similar structures except that melamine possesses an amino group and atrazine possesses a chlorine substituent. The two enzymes are functionally similar and catalyze hydrolytic displacement reactions as expected for this class of enzymes. Those of skill in the art, namely Seffernick et al., could readily recognize that these enzymes belonged to the class of bacterial amidohydrolases whose substrates may include s-triazine ring compounds with either amino group or chloro group substituents and assay their function accordingly. The two enzymes described by Seffernick et al. do not have "diverse function" as the Final Office Action implies.

Moreover, the Seffernick et al. reference is irrelevant. Applicants did not assert that the polypeptide of SEQ ID NO:1 was a bacterial aminohydrolase, and functional diversity among members of a protein family is expected to be class-specific. No evidence has been provided to support the assertion that the claimed genus is "large" and "variable" and has "diverse function."

D. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 16, 1999. Much has happened in the development of recombinant DNA technology in the 19 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:9, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

E. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claim and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claim of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claim is defined in terms of the chemical structure of SEQ ID NO:9. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claim is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable

advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

IV. Rejection of Claim 31 Under 35 U.S.C. § 112, first paragraph, enablement

The Examiner rejected Claim 31 under 35 U.S.C. §112, first paragraph, alleging that the "specification . . . does not reasonably provide enablement for a naturally-occurring polynucleotide which encodes a polypeptide of any function, wherein the polynucleotide is at least 80% sequence identical to the polynucleotide of SEQ ID NO:9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." (Final Office Action, page 5.)

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

A. How to make

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1 and 6-7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are described, for example, on page 18, line 28 through page 19, line 15, page 20, lines 29-32, and page 21, lines 4-12. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1, 3, and 4. Chemical and structural features of MITP-1 are described, for example, in Table 2. "Naturally occurring" polynucleotide sequences occur in nature; they are not created exclusively in a laboratory. The Specification describes how to find naturally occurring analogs and homologs in other individuals and species (e.g., page 39, lines 3-6) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9" scope (e.g., page 11, line 22 through page 12, line 32). The making of the claimed polynucleotides by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 21, lines 31-35, page 23, lines 21-25, page

24, lines 14-16, and page 34, lines 24-31. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to use

Applicants' invention is directed, *inter alia*, to polynucleotides encoding polypeptides having homology to bovine PSST subunit of the NADH-ubiquinone oxidoreductase complex (g599691). These polynucleotides have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of SEQ ID NO:1 (MITP-1), for toxicology testing, and for drug discovery (see the Specification at, e.g., page 38, line 25 through page 41, line 24). As described in the Specification (e.g., Tables 1, 2, 3, and 4) the sequence of the claimed SEQ ID NO:9 polynucleotide was identified in clone 1676225 from the cDNA library BLADNOT05 derived from bladder tissue. cDNA fragments 1510924F6 (LUNGNOT14), 1676225F6 (BLADNOT05), 1676225H1 (BLADNOT05), 1988463R6 (LUNGAST01), and 3143066H1 (HNT2AZS07) were used to assemble the consensus nucleotide sequence of SEQ ID NO:9. The SEQ ID NO:1 polypeptide has 213 amino acid residues and contains a respiratory-chain NADH dehydrogenase 20kD subunit signature sequence from V91 through E204. Electronic northern analysis of the SEQ ID NO:9 polynucleotide sequence shows expression in nervous, reproductive, and cardiovascular tissues and in tissues associated with cell proliferation and inflammation/immune.

Claim 31 stands rejected under 35 U.S.C. §112, first paragraph, based on the allegation that the use of the claimed polynucleotide variants is not adequately enabled. The rejection alleges in particular that "[t]he scope of the claim is not commensurate with the enablement provided in regard to the large number of naturally-occurring polynucleotides encoding proteins of different functions which have not been described and for which there is no specific use disclosed." (Final Office Action, page 6.) The Examiner alleges that "the specification fails to provide any guidance as to how one of skill in the art can (1) determine other functions for the claimed polynucleotides, and (2) how to use those polynucleotides without undue experimentation" citing that "[t]he state of the art clearly teaches the unpredictability of

determining function of structural homologs based on sequence homology." (Final Office Action, page 6.)

The rejection of Claim 31 is improper, as the invention of that claim is enabled and has a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in human bladder tissue, as well as variants of the SEQ ID NO:9 polynucleotide (hereinafter "the claimed polynucleotides"). The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of PSST subunits of the NADH:ubiquinone oxidoreductase complex (Specification, Table 2 and pages 1-2.) The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptides coded for by the claimed polynucleotides actually function. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this brief the Declaration of Dr. Tod Bedilion[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the enablement and utility of the claimed polynucleotides are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on March 16, 1999] that cDNA microarrays that contained the claimed polynucleotides, including the claimed Yue '867 application SEQ ID NO:9 polynucleotide variant, would be more useful tools than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or

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[1]The Bedilion Declaration is filed herewith in unexecuted form. The executed Declaration will be filed as soon as it is available.

actual) drugs for treating disorders of cell proliferation, inflammation, and immune response for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed variant polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed variant polynucleotides cannot be useful without precise knowledge of their biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the proteins encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise function.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §112. This is particularly so with respect to the uses of the claimed polynucleotides for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that the gene expression monitoring results obtained using the SEQ ID NO:9 polynucleotide variants are allegedly "meaningless" or otherwise insufficient to constitute adequate uses for the SEQ ID NO:9 polynucleotide variants (Final Office Action, e.g., page 9). In addition, a new rejection under 35 U.S.C. §112 on the basis of written description was made (see section III supra).

Under the circumstances, Applicants are submitting with this Response a Declaration of Dr. Tod Bedilion under 37 C.F.R. § 1.132 (the Bedilion Declaration). As we will show, the Bedilion Declaration shows the many substantial reasons why the Examiner's new positions and arguments, in particular with respect to the use of the claimed polynucleotides in a cDNA microarray, are without merit, and that the ignored toxicology disclosure should have been given additional and more adequate consideration.

The fact that the Bedilion Declaration is being submitted in response to positions taken and arguments made for the first time in the Final Office Action constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why that Declaration was not earlier submitted and should be admitted at this time.

1. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not

convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

2. Uses of the claimed polynucleotides for diagnosis of conditions and disorders characterized by expression of MITP-1, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail,

in the Bedilion Declaration accompanying this Response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

a. The uses of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility and enablement for the claimed polynucleotides.

The instant application (the Yue '867 application) claimed the benefit under 35 U.S.C. § 119(e) of provisional application United States Serial No. 60/124,655 filed on March 16, 1999 (hereinafter "the Yue '655 application"), having essentially the identical specification, with the exception of corrected typographical errors and reformatting changes. Thus page and line numbers may not match as between the Yue '867 application and the Yue '655 application. The SEQ ID NO:9 sequence recited in the Yue '867 application claims was first disclosed in the Yue '655 application and listed as SEQ ID NO:10 in the Yue '655 application. In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Yue '655 application on March 16, 1999 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[2]

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[2]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Yue '655 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as northern analysis, that

In connection with his explanations, Dr. Bedilion states that the "specification of the Yue '655 application would have led a person skilled in the art on March 16, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of disorders of cell proliferation, inflammation, and immune response to conclude that a cDNA microarray that contained the claimed polynucleotides, including the claimed Yue '867 application SEQ ID NO:9 polynucleotide variant, would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the claimed polynucleotides, including the claimed Yue '867 application SEQ ID NO:9 polynucleotide variant." (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on March 16, 1999] that cDNA microarrays that contained the claimed polynucleotides, including the claimed Yue '867 application SEQ ID NO:9 polynucleotide variant, would be more useful tools than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating disorders of cell proliferation, inflammation, and immune response for such purposes as evaluating their efficacy and toxicity. " *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-March 16, 1999 publications showing the state of the art on March 16, 1999 (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include more than three pages of text and six subparts ((a)-(f)), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on March 16, 1999 (and for several years prior to March 16, 1999) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Yue '655 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

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predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Yue '655 application at the time it was filed "would have wanted their cDNA microarray to have a [claimed polynucleotide, including the SEQ ID NO:9 variant] probe . . . because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to March 16, 1999." (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Yue '655 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities and adequate uses for the claimed polynucleotides.

Nowhere does the Patent Examiner address the fact that, as described on page 41, lines 14-24 and page 48, line 18 through page 49, line 2 of the instant application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-March 16, 1999 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Yue '655 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S.

Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the Yue '655 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
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> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original.)

John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 2):

In a pre-March 16, 1999 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 3). (emphasis added.)

b. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., (Reference No. 2, *supra*):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 2, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis

24:153-159 (1999) (Reference No. 4); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 5). .

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip. (Reference No. 4, page 156.)

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 6, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 7), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

c. The similarity of the polypeptides encoded by the claimed polynucleotide variants to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility and enablement of the use of the claimed polynucleotide variants can be imputed based on the relationship between the polypeptides they encode and another polypeptide of unquestioned utility, the SEQ ID NO:1 polypeptide. The polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded by the claimed invention has utility similar to the SEQ ID NO:1 polypeptide. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polynucleotide variants are at least 80% identical to SEQ ID NO:9 over the entire length of SEQ ID NO:9. This is more than enough homology to demonstrate a reasonable probability that the utility of polypeptide encoded by SEQ ID NO:9 can be imputed to the claimed polynucleotide variants (through the polypeptides they encode). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et al., Reference No. 1, *supra.*)

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Most important, none contradicts Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Based on the references of Bork (Genome Research, 10:398-400, 2000) van de Loo et al. (Proc. Natl. Acad. Sci. U.S.A. 92:6743-6747, 1995) Seffernick et al. (2001; J. Bacteriol. 183:2405-2410), and Broun et al. (Science 282:1315-1317, 1998), it is suggested that "[t]he state of the art clearly teaches the unpredictability of determining function of structural homologs based on sequence homology." (Final Office Action, page 6). However, Applicants respectfully disagree.

In a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

Contrary to the assertions of the Office Action, the use of such sequence comparisons to predict protein function is supported by the Bork reference, cited by the Office Action. The Bork reference discloses a 70% accuracy rate in bioinformatics-based predictions. This more than

meets the legal standard of utility, which requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics-based predictions.

van de Loo et al. describe the cloning of a fatty acyl hydroxylase based on sequence homology between certain fatty acyl hydroxylases and fatty acyl desaturases. In this example, the authors characterize fatty acyl hydroxylases and fatty acyl desaturases as catalyzing similar reactions (e.g., van de Loo et al., page 6743, right column, last paragraph), and conclude that the reaction mechanisms of oleate 12-hydroxylase and oleate desaturase are similar based on the sequence homology between them (e.g., van de Loo et al., abstract). The Broun et al. reference relates to the same two enzymes, fatty acyl hydroxylases and fatty acyl desaturases. Since the functions of the oleate 12-hydroxylase and oleate desaturase described by van de Loo et al. and Broun et al. are similar, it is not surprising that they share 67% sequence homology.

Accordingly if Applicants had asserted that the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase, then the Examiner would have provided evidence that the assignment to this family of fatty acyl hydroxylases may be incorrect. However, applicants did not assert the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase or a fatty acyl desaturase. Therefore, the van de Loo et al. and Broun et al. references are irrelevant and are not scientific evidence that the polypeptide of SEQ ID NO:1 is not a member of the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex.

The Seffernick et al. reference describes two enzymes, a melamine deaminase and an atrazine chlorohydrolase, that are 98% identical, yet have different substrate specificities. These two enzymes belong to a class of bacterial amidohydrolases whose members are known to catalyze the hydrolytic displacement of amino groups or chlorine substituents from triazine ring compounds. Notably, the substrates of the two enzymes, melamine and atrazine, have similar structures except that melamine possesses an amino group and atrazine possesses a chlorine substituent. The two enzymes are functionally similar and catalyze hydrolytic displacement reactions as expected for this class of enzymes. Those of skill in the art, namely Seffernick et al., could readily recognize that these enzymes belonged to the class of bacterial amidohydrolases whose substrates may include s-triazine ring compounds with either amino group or chloro group

substituents and assay their function accordingly. The two enzymes described by Seffernick et al. do not have "diverse function" as the Final Office Action implies.

Moreover, the Seffernick et al. reference is irrelevant. However, Applicants did not assert that the polypeptide of SEQ ID NO:1 was a bacterial aminohydrolase, and functional diversity among members of a protein family is expected to be class-specific. No evidence has been provided to support the assertion that the claimed genus is "large" and "variable" and has "diverse function."

The Examiner must accept Applicants' demonstration that the homology between the claimed polynucleotide variants and the SEQ ID NO:9 polynucleotide demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

d. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotides and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotides and its use of those polynucleotides on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

3. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established uses for the claimed polynucleotides are not enabled. (Office Action at pages 5-10.) The Examiner is incorrect both as a matter of law and as a matter of fact.

a. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological "function" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip*

Inc. v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

b. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotides encodes polypeptides in the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides, the Examiner refused to impute the utility of the members of the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides to the polypeptides encoded by the claimed polynucleotides.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain.a substantial number of useless members. So long as the class does not contain

a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses the polypeptides encoded by the claimed polynucleotides as if the general classes in which they are included are not the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides does not. The family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that the polypeptides encoded by the claimed polynucleotides would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the polypeptides encoded by the claimed polynucleotides are useful. It follows that the claimed polynucleotides also are useful.

c. Because the uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotides themselves, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays and chromosomal mapping (Specification, page 38, line 25 through page 42, line 16).

d. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention: Biological function, disease association, and differential expression are irrelevant to enablement of the use of the claimed polynucleotides

The Examiner states that "the specification fails to disclose the specific diseases, conditions and/or biological processes associated with the expression of naturally-occurring polynucleotides encoding proteins of any function encompassed by the claim" and "the specification fails to disclose which are the expression levels associated with a particular disease/condition or which mutations in the claimed polynucleotides are indicative of a disease and/or condition," and therefore "it is unclear how the claimed polynucleotides can be used as disease markers or as target for drug discovery or toxicology testing." (Final Office Action, page 9, emphasis in original.)

Applicants have demonstrated a utility for the claimed polynucleotides irrespective of whether or not a person would wish to perform additional experimentation on biological function or associated "biological processes" as another utility. The fact that additional experimentation could be performed to determine the functionality of the claimed polynucleotides or the

polypeptides encoded by the claimed polynucleotides does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the specific function of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The Examiner confuses use with function.

Applicants need not demonstrate whether the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides, are differentially expressed or associated with any disease, only whether the claimed polynucleotides or their encoded polypeptides are useful. The claimed polynucleotides and the polypeptides encoded by the claimed polynucleotides are useful whether or not the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are differentially expressed or associated with any disease.

The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. Monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or polypeptide, regardless of the differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to **other** polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides.

4. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website

www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases

in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § IV.B.3.b. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § IV.B.3.b. Thus the Training Materials cannot be applied consistently with the law.

V. Rejection of Claim 31 Under 35 U.S.C. § 102(b) as Being Anticipated by Hyslop

The Examiner rejected Claim 31 under 35 U.S.C. §102(b) as being anticipated by Hyslop et al. (Genomics 37:375:380, 1996), alleging the Hyslop sequence anticipated the claimed polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9.

In order to expedite prosecution, Claim 31 is amended to:

An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:9,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9,
c) a polynucleotide completely complementary to a polynucleotide of a),
d) a polynucleotide completely complementary to a polynucleotide of b), and
e) an RNA equivalent of a)-d).

Hyslop does not teach an isolated polynucleotide comprising a naturally occurring polynucleotide sequence having at least 80% sequence identity to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO:9 . Therefore Hyslop does not anticipate Claim 31. A naturally occurring polynucleotide sequence having at least 80% sequence identity to a polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9 is supported in the Specification, e.g., at page 12, lines 22-28. 78% = 648-3 = Hyslop / 824 = SEQ ID 9

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the prior art rejection over Hyslop.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding **objections and rejections.** Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent below.

If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

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Enclosures:

1. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078
2. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999)
3. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947
4. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999)
5. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000)
6. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999)
7. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 24 and 25 have been canceled.

Claims 3, 4, 5, 6, 8, and 31 have been amended as follows:

3. (Twice Amended) An isolated polynucleotide encoding a polypeptide [selected from the group consisting of:

a) a polypeptide] comprising the [an] amino acid sequence [selected from the group consisting] of SEQ ID NO:1 [SEQ ID NO:1-8,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2-8, and

c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:2-8].

4. (Twice Amended) The [An] isolated polynucleotide of claim 3 comprising the [a] polynucleotide sequence [selected from the group consisting] of SEQ ID NO:9 [SEQ ID NO:9-16].

5. (Once Amended) A recombinant polynucleotide comprising a promoter sequence operably linked to the [a] polynucleotide of claim 3.

6. (Once Amended) A cell transformed with the [a] recombinant polynucleotide of claim 5.

8. (Twice Amended) A method for producing the [a] polypeptide encoded by the polynucleotide of claim 3, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said

recombinant polynucleotide comprises a promoter sequence operably linked to the [a] polynucleotide of claim 3, and

b) recovering the polypeptide so expressed.

31. (Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:9,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9,

c) a polynucleotide completely complementary to a polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).